

## CADTH Reimbursement Recommendation

# Finerenone (Kerendia)

**Indication:** Kerendia (finerenone) as an adjunct to standard-of-care therapy in adults with chronic kidney disease and type 2 diabetes to reduce the risk of:

- end-stage kidney disease and a sustained decrease in estimated glomerular filtration rate
- cardiovascular death, nonfatal myocardial infarction, and hospitalization for heart failure.

**Sponsor:** Bayer Inc.

**Final recommendation:** Reimburse with conditions

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## What Is the CADTH Reimbursement Recommendation for Kerendia?

CADTH recommends that Kerendia be reimbursed by public drug plans as an adjunct to standard-of-care therapy in adult patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) to reduce the risk of end-stage kidney disease (ESKD) and a sustained decrease in estimated glomerular filtration rate (eGFR), and cardiovascular death, nonfatal myocardial infarction, and hospitalization for heart failure, if certain conditions are met.

## Which Patients Are Eligible for Coverage?

Kerendia should only be covered to treat patients with CKD and T2D, with eGFR levels of at least 25 mL/min/1.73 m<sup>2</sup>, and have too much albumin in their urine. Kerendia should not be covered for patients with chronic heart failure or who are being treated with a mineralocorticoid receptor antagonist (e.g., spironolactone).

## What Are the Conditions for Reimbursement?

Kerendia should only be reimbursed if prescribed in consultation with a nephrologist with experience in diagnosing and managing patients with CKD and T2D and if the cost of Kerendia is reduced.

## Why Did CADTH Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that patients with CKD and T2D treated with Kerendia experienced reduction in the risk of developing ESKD and cardiovascular events compared with placebo.
- Kerendia may address some needs that are important to patients because it reduces the risk of progression to kidney failure and the risk of cardiovascular events.
- Based on CADTH's assessment of the health economic evidence, Kerendia does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Kerendia is estimated to cost the public drug plans approximately \$148 million over the next 3 years.

## Additional Information

### What Is Chronic Kidney Disease?

CKD involves a gradual loss of kidney function. It is the leading cause of kidney failure, ultimately requiring dialysis or kidney transplant. Diabetes is the most common cause of kidney disease in Canada, and it is estimated that there were more than 1 million people in Canada living with CKD and T2D in 2022. Clinical diagnosis of CKD in people living with diabetes is based on albuminuria and/or decreased eGFR.

### Unmet Needs in Chronic Kidney Disease

Patients with CKD and T2D need effective treatments that prevent progression to ESKD and reduce the risk of cardiovascular events.

### How Much Does Kerendia Cost?

Treatment with Kerendia is expected to cost approximately \$1,219 per patient per year.

## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that finerenone be reimbursed as an adjunct to standard-of-care (SOC) therapy in adults with chronic kidney disease (CKD) and type 2 diabetes (T2D) to reduce the risk of end-stage kidney disease (ESKD) and a sustained decrease in estimated glomerular filtration rate (eGFR), and cardiovascular death, nonfatal myocardial infarction, and hospitalization for heart failure only if the conditions listed in [Table 1](#) are met.

## Rationale for the Recommendation

Two randomized, double-blind, active-controlled, phase III trials (FIDELIO, N = 5,734; FIGARO, N = 7,437) in adult patients with CKD and T2D demonstrated that when added to background therapy consisting of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) in combination with or without sodium-glucose cotransporter-2 (SGLT2) inhibitors, treatment with finerenone was associated with a statistically significant reduction in the risk of ESKD in FIDELIO trial and cardiovascular events compared with placebo plus SOC. The primary outcome in the FIDELIO trial was the time to the first occurrence of the 40% renal composite end point; the primary outcome of the FIGARO trial was the time to first occurrence of the cardiac composite end point. The first secondary outcome in each trial was the primary outcome of the other trial. In the FIDELIO trial, after 36 months of treatment, finerenone was associated with a 17.5% risk reduction in the time to the first occurrence of the 40% renal composite end point, with a hazard ratio (HR) of 0.825 (95% confidence interval [CI], 0.73 to 0.93; P = 0.0014) in favour of finerenone. In the FIGARO trial, after 48 months of treatment, the HR for this end point was 0.87 (95% CI, 0.76 to 1.01; P = 0.0689), which was not statistically significant. In the FIDELIO trial, finerenone was associated with a 14% risk reduction in the time to first occurrence of the cardiac composite end point, with an HR of 0.86 (95% CI, 0.75 to 0.99; P = 0.0339) in favour of finerenone, whereas in the FIGARO trial, finerenone was associated with a 13% risk reduction, with an HR of 0.87 (95% CI, 0.76 to 0.98; P = 0.0264) in favour of finerenone.

Patients and clinical experts identified a need for treatment options that reduce the risk of progression to kidney failure and cardiovascular events and improve health-related quality of life (HRQoL). CDEC concluded that, based on the evidence, finerenone appears to address some of the needs identified by patients by reducing the risk of progression to kidney failure and cardiovascular events; however, no definitive conclusions could be made regarding the effects of finerenone on the improvement of HRQoL.

Given the structure of the submitted economic model, CADTH could not produce a base-case estimation of the cost-effectiveness of finerenone; therefore, CDEC considered exploratory reanalyses conducted by CADTH, which considered the cost-effectiveness of finerenone relative to SOC using different assumptions. Based on the sponsor's submitted price for finerenone and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) ranged from \$70,052 to \$2,994,490 per quality-adjusted life-year (QALY) gained. The presence of a cardiovascular mortality benefit alongside the degree of dialysis reduction had the largest impact on the results. In all reanalyses, price reductions would be required for finerenone to achieve an ICER of \$50,000 per QALY.

**Table 1: Reimbursement Conditions and Reasons**

Reimbursement condition	Reason	Implementation guidance
<b>Initiation</b>		
1. Patients with CKD and T2D who have an eGFR level of at least 25 mL/min/1.73 m <sup>2</sup> and albuminuria level of at least 30 mg/g (or 3 mg/mmol).	At least 97% of the patients enrolled in the FIDELIO and FIGARO trials had an eGFR level of at least 25 mL/min/1.73 m <sup>2</sup> and albuminuria level of at least 30 mg/g.	CDEC noted that KDIGO guidelines define CKD as “persistently elevated urine albumin excretion (≥ 30 mg/g [3 mg/mmol] creatinine), persistently reduced estimated glomerular filtration rate (eGFR < 60 mL/min per 1.73 m <sup>2</sup> ), or both, for greater than 3 months.”
2. Treatment with finerenone must not be reimbursed in patients: <ul style="list-style-type: none"> <li>2.1. with CHF NYHA class II to IV or</li> <li>2.2. receiving an MRA.</li> </ul>	<p>Patients with clinical diagnosis of chronic heart failure with reduced ejection fraction and persistent symptoms (NYHA class II to IV) at the run-in visit were excluded from the FIDELIO and FIGARO trials.</p> <p>Patients who could not discontinue their MRA treatment at least 4 weeks before the screening visit were excluded from the FIDELIO and FIGARO trials.</p>	—
<b>Discontinuation</b>		
3. Treatment with finerenone must be discontinued if the patient has any of the following: <ul style="list-style-type: none"> <li>3.1. eGFR less than 15 mL/min/1.73 m<sup>2</sup></li> <li>3.2. UACR increased from baseline level while receiving finerenone.</li> </ul>	<p>Finerenone is contraindicated in patients with ESKD (eGFR &lt; 15 mL/min/1.73 m<sup>2</sup>).</p> <p>The change in UACR from baseline to month 4 was larger in the finerenone group than in the placebo group in both the FIDELIO and FIGARO studies.</p> <p>Based on clinical expert opinion, reduction in UACR is an appropriate surrogate marker to assess response in clinical practice.</p>	The clinicians must document UACR levels at start of therapy.
<b>Prescribing</b>		
4. Finerenone should be prescribed in consultation with a nephrologist with experience in the diagnosis and management of patients with CKD and T2D.	Based on clinical expert opinion, it would be appropriate for primary care clinicians in consultation with a nephrologist to prescribe finerenone.	—
<b>Pricing</b>		
5. A reduction in price.	Based on the exploratory reanalyses presented, the committee recommended that a price reduction of at least 55% would be needed to improve the probability that finerenone is cost-effective at a \$50,000 per QALY threshold. This was due to uncertainties with expected mortality benefits and the degree of dialysis reduction seen from finerenone relative to SOC.	—

Reimbursement condition	Reason	Implementation guidance
	Outstanding uncertainty remains because SOC in the trial was not reflective of current practice; therefore, it was noted that higher price reductions may be required.	
<b>Feasibility of adoption</b>		
6. The feasibility of adoption of finerenone must be addressed.	At the submitted price, the budget impact of finerenone is expected to be greater than \$40 million in years 2 and 3 if funded for all patients with CKD and T2DM, regardless of what treatments are included in SOC.	—

CHF = chronic heart failure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; KDIGO = Kidney Disease: Improving Global Outcomes; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; SOC = standard of care; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

## Discussion Points

- The sponsor requested a reconsideration of the initial draft recommendation to reimburse finerenone. CDEC discussed each issue identified by the sponsor in their request for reconsideration.
- During the reconsideration meeting, CDEC discussed the anticipated place in therapy for finerenone in clinical practice in Canada. CDEC considered information from the Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO) as well as the Clinical Practice Guidelines issued by the American Association of Clinical Endocrinology. CDEC noted that finerenone should only be reimbursed when prescribed in addition to SOC therapy in patients with CKD and T2D who have persistent albuminuria, with SOC defined as maximally tolerated doses of ACE inhibitor or ARB therapy in combination with an SGLT2 inhibitor, unless SGLT2 inhibitors are contraindicated or not tolerated.
- During the reconsideration meeting, CDEC noted that although both SGLT2 inhibitors and glucagon-like peptide 1 (GLP-1) have indications to improve glycemic control in adult patients with T2D, only SGLT2 inhibitors are currently indicated to reduce the risk of sustained eGFR decline, ESKD, and cardiovascular and renal death in adults with CKD.
- During the initial and reconsideration meetings, CDEC discussed the results from the subgroup of patients in the FIDELIO and FIGARO trials who were receiving either an ACE inhibitor or ARB in combination with an SGLT2 inhibitor. Due to the limited evidence, CDEC remained uncertain regarding the generalizability of results from the pivotal studies to patients who would receive finerenone as an add-on to either an ACE inhibitor or ARB in combination with an SGLT2 inhibitor; however, the clinical expert noted to CDEC there could be added benefit when finerenone is provided to patients with persistent albuminuria who are also receiving SGLT2 inhibitor therapy. In addition, CDEC noted that the reimbursement of finerenone might need to be reconsidered or adjusted once results from an ongoing study (the CONFIDENCE trial), which is assessing the treatment combination of finerenone and empagliflozin in adult patients with CKD and T2D, become available.
- The direct comparison of finerenone and SGLT2 inhibitors is limited by the small subpopulation included in the trials. A network meta-analysis (NMA) that compared

finerenone and SGLT2 inhibitors in patients with CKD and T2D with background treatment that included an ACE inhibitor or ARB concluded that SGLT2 inhibitors are more effective than finerenone at reducing kidney function progression and hospitalization due to heart failure events in this population. However, only 1 trial of the included 8 trials assessed finerenone, which limited the statistical power of this NMA and precluded drawing definitive conclusions about the comparative effectiveness of finerenone versus SGLT2 inhibitors.

- The FIDELIO and FIGARO trials were not powered to assess the risk of all-cause mortality and all-cause hospitalization; therefore, the effect of finerenone on these outcomes remains unknown.
- CDEC discussed that there was inconsistency between the FIDELIO and FIGARO trials in the results of the 40% renal composite outcome and noted that the FIDELIO trial enrolled patients who had lower eGFR and higher UACR at baseline than those enrolled in the FIGARO trial. In the FIDELIO trial, the mean baseline eGFR was approximately 44 mL/min/1.73 m<sup>2</sup> (standard deviation [SD] = 12.5 mL/min/1.73 m<sup>2</sup>) in both groups, and the mean baseline UACR was 798.8 mg/g (SD = 2.7 mg/g) and 814.7 mg/g (SD = 2.7 mg/g) in the finerenone and placebo groups, respectively; in the FIGARO trial, the mean baseline eGFR was approximately 68 mL/min/1.73 m<sup>2</sup> (SD = 21.7 mL/min/1.73 m<sup>2</sup>) in both groups and the mean baseline UACR was 284.3 mg/g (SD = 3.6 mg/g) and 288.9 mg/g (SD = 3.5 mg/g) in the finerenone and placebo groups, respectively. Approximately 88% of patients in the FIDELIO trial and 50.7% of patients in the FIGARO trial had very high albuminuria.
- CDEC discussed that maintaining and improving quality of life was identified as an outcome important to patients. However, the interpretation of HRQoL results is limited by the declining number of patients who completed these assessments over time and the lack of evidence of validity or minimal important difference for the Kidney Disease Quality of Life (KDQOL) and 5-Level EQ-5D questionnaires in patients with CKD and T2D; therefore, the effect of finerenone on HRQoL is unknown.
- The estimated price reduction for finerenone needed to achieve cost-effectiveness is uncertain. The SOC in the sponsor's pharmacoeconomic analysis, based on the FIDELIO trial, is not reflective of current SOC, which adds additional uncertainty to the analysis. CADTH's pharmacoeconomic analysis allows for clinically unsupported improvements in eGFR, reductions in strokes and myocardial infarctions that were not seen in the trial, and may overestimate cost savings from preventing cardiovascular events. Therefore, further price reductions may be required to ensure the cost-effectiveness of finerenone.
- CDEC noted the large potential budget impact of reimbursing finerenone, estimated to be \$148,282,507 over 3 years. Price negotiations and the implementation of discontinuation criteria could assist in reducing the budget impact.

## Background

Diabetes is the most common cause of kidney disease in Canada, and it is estimated by the sponsor that there are more than 1 million people in Canada living with CKD and T2D in 2022. Older age, low socioeconomic status, obesity, smoking, poor glycemic and blood pressure control, and genetic factors are known risk factors for diabetic kidney disease. CKD is the leading cause of kidney failure (previously termed "end-stage renal disease") necessitating dialysis or renal transplant; CKD is also associated with cardiovascular complications leading to decreased quality of life and premature death. In a US survey that evaluated

15,000 patients with diabetes and kidney disease, 10-year mortality for patients with both CKD and T2D was 4-fold and 2.7-fold higher compared with patients with CKD or T2D alone, respectively, and cardiovascular mortality was 3-fold and 6-fold higher, respectively. Patients with both CKD and T2D also reported lower HRQoL scores compared with those with CKD alone or T2D alone. CKD is clinically diagnosed in people living with diabetes based on the presence of albuminuria ( $> 30$  mg/g) and/or decreased eGFR ( $< 60$  mL/min/1.73 m<sup>2</sup>) in at least 2 of 3 assessments in a 3-month period. These are also 2 important indicators of disease progression: high UACR and low eGFR values indicate more severe disease.

According to the clinical experts consulted by CADTH, the primary goal of treatment is to reduce the risk of progression of CKD to ESKD by the application of pharmacologic and lifestyle strategies. The general approach to the management of patients with CKD and T2D includes optimization of blood pressure, glycemic control, dietary changes, reducing proteinuria, and lowering lipid levels with statins. For the past several decades, patients with CKD have been treated with either an ACE inhibitor or ARB that inhibit the renin-angiotensin-aldosterone system (RAAS). Recently, guidelines have been revised to encourage the use of SGLT2 inhibitors in patients with CKD and T2D, specifically for patients with severely increased albuminuria ( $> 300$  mg/g). Some patients may be intolerant to SGLT2 inhibitors, including patients with poor glycemic control, high risk of genital infections or lower limb amputation, or acute kidney injury. According to the clinical experts consulted by CADTH, there is limited access to SGLT2 inhibitors in Canada and access varies by jurisdictions, although access and subsequent use is expected to increase with time. In this review, the sponsor identifies SGLT2 inhibitors in addition to ACE inhibitors or ARBs as SOC. Despite the application of the pharmacologic and lifestyle strategies, the clinical experts indicated that there are still many patients with both CKD and T2D who continue to progress to kidney failure or develop cardiovascular events and that patients with CKD and T2D could benefit from additional pharmacologic therapies.

Finerenone has been approved by Health Canada as an adjunct to SOC therapy to reduce the risk of ESKD and a sustained decrease in eGFR, and cardiovascular death, nonfatal myocardial infarction, and hospitalization for heart failure. Finerenone is a nonsteroidal, selective mineralocorticoid receptor antagonist (MRA). It is available as oral tablets and the recommended starting dose of finerenone is 20 mg once daily for patients with an eGFR of at least 60 mL/min/1.73 m<sup>2</sup> or 10 mg once daily for patients with an eGFR of at least 25 mL/min/1.73 m<sup>2</sup> to less than 60 mL/min/1.73 m<sup>2</sup>. Four weeks after initiation or restart or up-titration of finerenone treatment, serum potassium and eGFR should be remeasured to determine continuation of finerenone treatment and dose adjustment. Thereafter, serum potassium should be remeasured periodically and as needed based on patient characteristics and serum potassium levels. Initiation of finerenone treatment is not recommended in patients with an eGFR less than 25 mL/min/1.73 m<sup>2</sup> or in patients with serum potassium greater than 5.0 mmol/L. Treatment should be discontinued in patients with ESKD (eGFR  $< 15$  mL/min/1.73 m<sup>2</sup>).

## Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of the 2 phase III, randomized, double-blind, placebo-controlled, clinical studies in patients with CKD and T2D
- patients perspectives gathered by patient groups, The Kidney Foundation of Canada and Diabetes Canada
- input from public drug plans that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with CKD and cardiovascular disease
- input from 1 clinician group, LMC Diabetes and Endocrinology
- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the Request for Reconsideration (described subsequently).

## Stakeholder Perspectives

### Patient Input

Patient input for the review of finerenone was provided as a joint submission from The Kidney Foundation of Canada and Diabetes Canada. They conducted an online survey of patients with CKD and T2D and their caregivers residing across Canada in May 2022 (N = 24; 9 completed and 15 partially completed the survey). A total of 8 respondents identified as people with CKD, 1 respondent identified as a caregiver of a person with CKD, and 6 respondents identified as people living with T2D.

Survey respondents who identified themselves as living with both CKD and T2D reported challenges with fatigue and anemia and with adhering to dietary restrictions due to their high costs and inconvenience when dining with others. People with CKD may often present with comorbidities; 7 respondents reported high blood pressure, 3 reported high cholesterol, 1 reported high potassium levels, 1 reported heart disease, and 1 reported having had a heart attack. One survey respondent stated feeling tired and unable to focus on certain tasks due to living with multiple medical conditions. Five respondents reported worsening of their CKD, and 6 respondents indicated they have taken a medication to reduce the risk of worsening kidney disease, of which 3 reported experiences with ACE inhibitors and 2 reported experience with ARBs. Respondents also indicated experience with diuretics, tacrolimus, erythropoietin, and dapagliflozin (an SGLT2 inhibitor). Of the 6 survey respondents who indicated their level of satisfaction with their current medication(s), 3 were satisfied, 1 was very satisfied, and 2 were neutral.

Survey respondents identified the following factors as the most important considerations for new treatment options in CKD: “does it make me feel tired,” “does it interfere with my other medications,” and “how much does it cost.” Survey respondents identified the following outcomes as important for new treatment options for both CKD with or without diabetes: “limiting or arresting the progression of both diseases,” “make kidneys better,” “a longer lifespan,” and “maintain and improve quality of life overall.”

The Kidney Foundation of Canada and Diabetes Canada indicated that patients living with CKD may experience significant financial challenges due to reduced income (e.g., missed time from work as a result of their symptoms) and increased expenses (e.g., high costs associated with treatment, frequent visits to the health care team, and hospitalization). According to the organizations, equitable access to medications that slow the progression of kidney disease and reduce the risk of cardiac events, such as finerenone, may help to relieve the financial burden of CKD and T2D on patients and the health care system.

## Clinician Input

### Input From Clinical Experts Consulted by CADTH

The clinical experts mentioned that despite available therapies for patients with CKD and T2D, there is a need for additional treatment options that reduce the risk of progression to kidney failure or cardiovascular events. There are still patients who continue to progress to these outcomes and that can benefit from additional therapies, such as finerenone. The clinical experts noted that the current paradigm aims to reduce progression of CKD to ESKD (kidney failure requiring dialysis or renal transplant). Treatment measures include blood pressure control, RAAS inhibition (ACE inhibitors and/or ARBs), and the use of SGLT2 inhibitors in addition to lifestyle changes, the use of statins, and glycemic control. The clinical expert noted that finerenone may be combined with SGLT2 inhibitors to reduce cardiorenal risk because they protect kidney function through distinct and complementary pathways.

According to the clinical experts, finerenone should be considered for patients who remain with a significant residual proteinuria despite being on a maximal tolerated dose of an ACE inhibitor or ARB and SGLT2 inhibitor and noted that finerenone can be added to these therapies 3 months after initiating an SGLT2 inhibitor based on clinical experience. They also mentioned that patients who are unable to tolerate SGLT2 inhibitors (e.g., due to hypotension or acute kidney injury) should be considered for finerenone. In the opinion of the clinical experts, treatment response can be assessed using surrogate measures such as changes in proteinuria over time, and stability of renal function (eGFR). Intervals for monitoring should follow the current guideline recommendations (twice annually according to the ADA).

According to the clinical experts, finerenone is better initiated as an add-on therapy in a specialist setting or in community setting but with specialist guidance and support. The clinical experts note that finerenone should be discontinued if the patient is unable to tolerate the drug because of adverse events (AEs) such as hyperkalemia not amenable to management (e.g., dietary changes and/or diuretics use) or hypotension.

### Clinician Group Input

The views of the clinician groups were consistent with the views of the clinical experts consulted by CADTH. Clinician group input for the review of finerenone was provided as a submission prepared by clinicians representing LMC Diabetes and Endocrinology, a single-specialty group endocrinology practice with 13 clinics across 3 provinces (Ontario, Quebec, and Alberta).

The clinician group recognized that there is an unmet need for a medication that will address the significant decline in kidney function and increased risk of cardiovascular disease in persons living with T2D despite the availability of RAAS blockers and SGLT2 inhibitors and in those who experience intolerance to or adverse effects with currently available treatment options. The clinician group indicated finerenone would be used as an add-on therapy to

RAAS blockers with or without SGLT2 inhibitors in persons living with T2D with an ongoing risk for kidney disease progression and developing cardiovascular disease. Alternatively, finerenone would be used as the first add-on therapy in patients who were unable to tolerate or developed adverse effects with RAAS blockers or SGLT2 inhibitors.

With respect to the patient population that will most likely benefit from finerenone, the clinician group identified patients with an eGFR of at least 25 mL/min/1.73 m<sup>2</sup> and a UACR of at least 34 mg/mmol or with an eGFR from 25 mL/min/1.73 m<sup>2</sup> to 90 mL/min/1.73 m<sup>2</sup> and a UACR from 3.4 mg/mmol to 33.9 mg/mmol. The patient population that was identified to be the least suitable for treatment with finerenone would be patients with a history of clinically significant hyperkalemia. Outcomes used in clinical practice would be preservation of eGFR over time, reduction in UACR, improved symptoms of heart failure or prevention of heart failure, and reduced emergency department visits or hospitalizations.

## Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially affect the implementation of a CADTH recommendation for finerenone:

- relevant comparators
- considerations for initiation of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- system and economic issues.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

**Table 2: Responses to Questions From the Drug Programs**

Implementation issues	Response
<b>Relevant comparators</b>	
Was placebo plus SOC a reasonable comparator to use in these studies? Could there have been an alternative?	CDEC agreed with the clinical experts consulted by CADTH that placebo plus SOC is a reasonable comparator.
The sponsor asked for reimbursement of the drug as adjunctive SOC for patients with CKD and T2D. Does CDEC agree with the SOC defined by the sponsor for the current landscape of therapy for CKD and T2D?  The sponsor indicated that SOC therapies include either an ACE inhibitor or ARB in combination with an SGLT2 inhibitor unless contraindicated or not tolerated.	CDEC agreed with the clinical experts consulted by CADTH that SOC as defined by the sponsor is appropriate.
The benefit status of SGLT2 inhibitors varies across the country, and in some is based on indication such as T2D and HF. Patients in jurisdictions that have SGLT2 inhibitors as restricted would have to meet specific criteria before adding on finerenone. Would the need for this drug in patients with CKD and T2D have an effect on the current benefit status of an SGLT2 inhibitor?	CDEC agreed with the clinical experts consulted by CADTH that the need for finerenone should not directly impact access to an SGLT2 inhibitor.

Implementation issues	Response
<p>The sponsor asked for reimbursement of finerenone to use as adjunctive care of therapy to reduce hospitalizations for HF? Could there be an indication creep and need to use this medication just in patients with HF?</p>	<p>The clinical experts noted that in cardiology, MRA drugs are a fundamental part of guideline-based therapy, and a newer-generation drug with relative advantages over spironolactone and eplerenone would be welcomed, regardless of whether the patient had CKD, T2D, or both. This would not be viewed as an “indication creep” so much as an indication.</p> <p>CDEC disagreed with the clinical experts and noted that finerenone is only indicated for adult patients with both CKD and T2D and any use for patients who do not have both CKD and T2D is off label, and that finerenone is appropriate therapy for patients with HF only when it has a Health Canada indication. In addition, FIGARO and FIDELIO excluded patients with a clinical diagnosis of chronic HF with reduced ejection fraction and persistent symptoms (NYHA class II to IV) at the run-in visit.</p>
<p>Would there be a need for finerenone in patients with either CKD or T2D alone? If so, how would jurisdictions be expected to handle these requests?</p>	<p>The clinical experts noted that there would be a need for finerenone for patients with CKD or T2D alone only in situations in which ACE inhibitors or ARBs and/or SGLT2 inhibitors are not tolerated or, in rare instances, contraindicated. The prescribers can state these reasons to justify access to the medication as needed. This will rarely happen based on current clinical practice experience because there are no data to inform this question.</p> <p>The sponsor also noted that that there are no data to inform whether finerenone can be used in patients with either CKD or T2D alone; therefore, treatment in this manner is expected to be rare in current clinical practice. The Health Canada indication is for patients with both CKD and T2D; therefore, use in CKD alone would be off label. A clinical trial planned specifically to evaluate finerenone in the patient populations with CKD and without diabetes, is expected to be completed in 2025.</p> <p>CDEC noted that finerenone is only indicated for adult patients with both CKD and T2D, and that finerenone should not be reimbursed for patients with CKD or T2D alone.</p>
<p>The sponsor acknowledges that since the conclusion of both trials, Canadian treatment practices have evolved for CKD and T2D; SGLT2 inhibitors have received regulatory approvals and contemporary guidelines recommend their use to reduce cardiorenal risk in CKD and T2D.</p> <ul style="list-style-type: none"> <li>• Forxiga is currently the only SGLT2 inhibitor currently indicated for patients with CKD with or without diabetes.</li> <li>• There is an ongoing study for the indication to be reviewed by CADTH in which the intervention is a combination of finerenone and empagliflozin.</li> <li>• Would there be a preference for the requirement of one SGLT2 inhibitor over another when adding on finerenone? Would any SGLT2 inhibitor be reasonable as defined by SOC?</li> </ul>	<p>CDEC agreed with the clinical experts that the beneficial effects of SGLT2 inhibitors on renal outcomes in people with T2D are largely seen as a “class effect” at this point. Data are limited in this regard in people without diabetes to be conclusive.</p>

Implementation issues	Response
Can the committee define intolerance or contraindication to a SGLT2 inhibitor?	CDEC agreed with the clinical experts that intolerance or contraindication to an SGLT2 inhibitor is defined as patients with persistent hypoglycemia or hypotension, acute kidney injury, and high risk of amputation.
<b>Considerations for initiation of therapy</b>	
What would CDEC's definition of CKD be for patients to meet initiation criteria? Are there specific lab markers or other parameters that would be required from patients?	<p>The clinical experts indicated that the definition of CKD for patients to meet initiation criteria is if they have CKD and persistent residual risk (albuminuria) despite an optimal use of an ACE inhibitor or ARB and an SGLT2 inhibitor. The use of finerenone will be an add-on therapy to modify risk in CKD in patients already optimized on the SOC (ACE inhibitor or ARB plus SGLT2 inhibitor) and having serum potassium in the normal range (&lt; 5 mmol/L)</p> <p>CDEC noted that KDIGO guidelines define CKD as "persistently elevated urine albumin excretion (<math>\geq 30</math> mg/g [3 mg/mmol] creatinine), persistently reduced estimated glomerular filtration rate (eGFR &lt; 60 mL/min per 1.73 m<sup>2</sup>), or both, for greater than 3 months."</p>
<b>Considerations for discontinuation of therapy</b>	
What would CDEC define as disease progression for CKD and when would the medication be discontinued?	<p>CDEC agreed with the clinical experts that the key factor that may drive discontinuation will be hyperkalemia. This will usually be on a temporary basis to control the hyperkalemia with dietary measures, and then reassess and reinstate therapy. A permanent discontinuation is only warranted in case of hyperkalemia that is persistent and not amenable to dietary and/or therapeutic measures as is done with ACE inhibitors or ARBs.</p> <p>CDEC also noted that patients who progress to ESKD who require dialysis or transplant should discontinue finerenone.</p>
If the patient had a clinically significant CV event or hospitalization due to HF while on finerenone, would treatment be discontinued?	CDEC agreed with the clinical experts that if the patient had a clinically significant CV event or hospitalization due to HF while on finerenone, treatment with finerenone should not be discontinued because finerenone would be used in lieu of an older MRA. Patients with HF have readmissions for HF or admissions for other cardiac conditions (e.g., arrhythmia) while on an MRA, and these drugs are not stopped just because of that. In the specific example of arrhythmia, if this was VT or VF thought to be due to hyperkalemia that was due in turn to the MRA, then dosing might be adjusted, but it would not mean that the drug would automatically be stopped.
<b>Considerations for prescribing of therapy</b>	
<p>Would this medication only be prescribed by a specialist, or would a general practitioner be able to initiate therapy?</p> <p>If only a specialist, which would be the most appropriate (cardiologist, nephrologist, or endocrinologist)?</p>	CDEC agreed with the clinical experts that general practitioners will be prescribing the medication because they see the most patients meeting the eligibility criteria for the drug (i.e., CKD with albuminuria and T2D).

Implementation issues	Response
<b>System and economic issues</b>	
<ul style="list-style-type: none"> <li>The submitted price per smallest dispensable unit of Kerendia is \$3.3400 per 10 mg or 20 mg tablet, which corresponds to a total cost of \$3.3400 per day (once daily dosing).</li> <li>Listing this drug as requested is estimated to result in incremental costs to the pan-Canadian public drug programs (excluding Quebec) of \$12,491,153 in year 1, \$36,394,767 in year 2, and \$59,588,681 in year 3.</li> </ul> <p>With generic SGLT2 inhibitors coming out soon, would this have any impact on the substantial estimated incremental costs to the drug programs provided by the sponsor?</p>	<p>CDEC noted the large potential budget impact of reimbursing finerenone: \$148,282,507 over 3 years. Price negotiations and the implementation of discontinuation criteria could assist in reducing the budget impact.</p>

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CDEC = CADTH Canadian Drug Expert Committee; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HF = Heart failure; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter-2; SOC = standard of care; T2D = type 2 diabetes; VF = ventricular fibrillation; VT = ventricular tachycardia.

## Clinical Evidence

### Pivotal Studies and Protocol-Selected Studies

#### Description of Studies

FIDELIO (N = 5,734) and FIGARO (N = 7,437) are phase III, randomized, double-blind, placebo-controlled, parallel-group, multicentre, event-driven studies of finerenone compared with placebo in patients with CKD and T2D. The 2 studies differed in their primary objective: the primary objective in the FIDELIO trial was time to the first occurrence of a renal composite end point in both the finerenone and placebo groups, while the primary objective of the FIGARO trial was time to the first occurrence of the cardiovascular composite end point in both the finerenone and placebo groups. Secondary objectives in each study included the primary objective of the other study, as well as time to first occurrence of a more severe renal composite end point, time to all-cause mortality, time to all-cause hospitalization, and change in UACR from baseline to month 4. The studies were sponsored by Bayer and included 30 (FIDELIO) and 31 (FIGARO) study centres in Canada.

After a run-in period of up to 16 weeks and a screening period up to 2 weeks, eligible patients were randomized in a 1:1 ratio to the finerenone (10 mg or 20 mg) or placebo treatment arm, and stratified by region, eGFR category at screening, and albuminuria interval at screening. Randomization occurred at visit 1 and then there were 3 more planned monthly visits, followed by a visit every 4 months until the end of the study. Finerenone drug dose could be uptitrated or downtitrated at any point following start of treatment at visit 1. If patients stopped the study drug prematurely, they remained in the trial and were followed up until the end of the study.

Patient demographic characteristics and key disease characteristics were balanced between the finerenone and placebo groups in both trials. The mean age in both groups in both studies was approximately 65 years. Most patients in both trials were male (69.8% were males and 30.2% were females) and white (68.1%). Mean baseline body mass index across all groups was 31.3 kg/m<sup>2</sup> (SD = 6.0 kg/m<sup>2</sup>), 47.5% of patients had never smoked, and 59.8% were

abstinent from alcohol. In the FIDELIO trial, mean baseline eGFR was approximately 44 mL/min/1.73 m<sup>2</sup> (SD = 12.5 mL/min/1.73 m<sup>2</sup>) in both groups and mean baseline UACR was 798.8 mg/g (SD = 2.7 mg/g) and 814.7 mg/g (SD = 2.7 mg/g) in the finerenone and placebo groups, respectively. In the FIGARO trial, mean baseline eGFR was approximately 68 mL/min/1.73 m<sup>2</sup> (SD = 21.7 mL/min/1.73 m<sup>2</sup>) in both groups, and mean baseline UACR was 284.3 mg/g (SD = 3.6 mg/g) and 288.9 mg/g (SD = 3.5 mg/g) in the finerenone and placebo groups, respectively. Regarding medication use at baseline, 66% of patients in the FIDELIO trial and 57% of patients in the FIGARO trial were on ARBs, and 34% of patients in the FIDELIO trial and 43% of patients in the FIGARO trial were on ACE inhibitors. Across the 2 trials, 97.7% of patients were also on treatment for diabetes, including 6.7% of patients who were on SGLT2 inhibitors.

## Efficacy Results

In the FIDELIO trial, the primary and key secondary end points met the preplanned criteria for significance and all-cause mortality, the next secondary end point was tested hierarchically and it did not reach statistical significance, so the remaining secondary end points were tested in an exploratory manner. In the FIGARO trial, the primary end point met the preplanned criteria for significance and the key secondary end point did not; therefore, the remaining secondary end points were tested in an exploratory manner.

The primary outcome in the FIDELIO study was time to first occurrence of the 40% renal composite end point comprising onset of kidney failure, a sustained decrease of eGFR of 40% or more from baseline over at least 4 weeks, or renal death, which is referred to as the “40% renal composite end point” hereafter. The 40% renal composite end point was a key secondary end point in the FIGARO trial. In the FIDELIO trial, this composite outcome occurred in 504 (17.8%) patients and 600 (21.1%) patients in the finerenone and placebo groups, respectively; the HR was 0.825 (95% CI 0.73 to 0.93, P = 0.0014) in favour of finerenone. In the FIGARO trial, this end point occurred in 350 (9.5%) patients and 395 (10.8%) patients in the finerenone and placebo groups, respectively; the HR was 0.87 (95% CI, 0.76 to 1.01; P = 0.0689), which was not statistically significant. In the pooled analysis of the FIDELIO and FIGARO trials, the HR was 0.85 (95% CI, 0.77 to 0.93) and 0.77 (95% CI, 0.67 to 0.88) for the 40% and 57% renal composite end points, respectively, in favour of finerenone.

The 57% renal composite end point was a secondary end point in both studies. In the FIDELIO trial, it occurred in 252 (8.9%) patients and 326 (11.5%) patients in the finerenone and placebo groups respectively; the HR was 0.76 (95% CI 0.65 to 0.90) in favour of finerenone. In the FIGARO trial, it occurred in 108 (2.9%) patients and 139 (3.8%) patients in the finerenone and placebo groups, respectively; the HR was 0.77 (95% CI 0.60 to 0.99) in favour of finerenone. In the FIDELIO trial, the individual components of sustained decrease in an eGFR of 40% or more and an eGFR at least 57% (relative to baseline) had HRs of 0.815 (95% CI, 0.722 to 0.920) and 0.68 (95% CI, 0.55 to 0.82), respectively; these were the main drivers of the composite outcome results. The treatment effect of finerenone was assessed across the following subgroups of patients: history of cardiovascular disease, eGFR category at baseline, type of albuminuria at baseline, and SGLT2 inhibitor treatment at baseline. In general, the treatment effect of finerenone on the primary end point (time to first occurrence of the 40% renal composite end point) was consistent with the primary analysis across patient subgroups with the following exception: In the FIDELIO trial, HR was greater than 1 in patients who were treated with SGLT2 inhibitors at baseline, favouring placebo over finerenone, yet the small sample size and wide CIs in this subgroup reflects uncertainty in the effect estimates. In the FIGARO trial, HR was also greater than 1 in patients with an eGFR from 45 mL/min/1.73 m<sup>2</sup>

to less than 60 mL/min/1.73 m<sup>2</sup> at baseline and in patients with high albuminuria (30 mg/g to < 300 mg/g) at baseline.

Baseline values of UACR were comparable between the treatment groups but differed between trials according to the inclusion criteria, with higher values in the FIDELIO trial population. In both trials, the change in UACR from baseline to month 4 was larger in the finerenone group than in the placebo group, with a ratio of least squares (LS) mean change from baseline of 0.69 (95% CI, 0.66 to 0.72) and 0.68 (95% CI, 0.65 to 0.70) in the FIDELIO and FIGARO trials, respectively, with a P value less than 0.0001.

Baseline values of eGFR were comparable between the treatment groups but differed between trials according to the inclusion criteria, with lower values in the FIDELIO trial population. There was a larger acute reduction in eGFR in the finerenone group than in the placebo group, with an LS mean difference between groups at month 4 of -2.38 (95% CI, -2.77 to -1.98) and -2.24 (95% CI, -2.67 to -1.80) in the FIDELIO and FIGARO trials, respectively, with a P value of less than 0.0001. The decrease in eGFR in the finerenone group then slowed down until the difference between both groups became positive, indicating a slower rate in eGFR decline rate in the finerenone group than in the placebo group at month 28 in the FIDELIO trial and month 36 in the FIGARO trial.

The primary outcome in the FIGARO study was time to first occurrence of the cardiac composite end point comprising cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure. The cardiovascular composite end point was a key secondary end point in the FIDELIO trial. In the FIDELIO trial, this composite outcome occurred in 367 (13%) patients and 420 (14.8%) patients in the finerenone and placebo groups, respectively; the HR was 0.86 (95% CI 0.75 to 0.99, P = 0.0339) in favour of finerenone. In the FIGARO trial, this end point occurred in 458 (12.4%) patients and 519 (14.2%) patients in the finerenone and placebo groups, respectively; the HR was 0.87 (95% CI, 0.76 to 0.98, P = 0.0264) in favour of finerenone. In the pooled analysis of both trials, the HR was 0.86 (95% CI, 0.78 to 0.95) with P value of 0.0018 in favour of finerenone. In the FIGARO trial, the only individual component of statistical significance was hospitalization due to heart failure with an HR of 0.71 (95% CI, 0.56 to 0.90) in favour of finerenone. In both trials, there was almost no difference in the risk of nonfatal stroke with an HR of 0.97 (95% CI, 0.74 to 1.26) in the FIDELIO trial and 1.03 (95% CI, 0.77 to 1.38) in the FIGARO trial. The treatment effect of finerenone on the time to first occurrence of the cardiac composite end point was assessed across the following subgroups of patients: history of cardiovascular disease, eGFR category at baseline, type of albuminuria at baseline, and SGLT2 inhibitor treatment at baseline. In general, the treatment effect of finerenone was consistent with the primary analysis across patient subgroups with the following exception: HR was approximately 1 in patients who were treated with SGLT2 inhibitors at baseline in the FIDELIO trial, whereas the HR was 0.49 (95% CI, 0.28 to 0.86) in the FIGARO trial. However, the small sample size of this patient group in both trials reflects uncertainty in the effect estimates.

Incidence of all-cause mortality was similar between both groups in both trials, with 552 (8.5%) deaths and 614 (9.4%) deaths from any cause in the finerenone and placebo groups, respectively. Comparing the finerenone group with the placebo group, the HR was 0.90 (95% CI 0.75 to 1.07) in the FIDELIO trial and 0.89 (95% CI, 0.77 to 1.04) in the FIGARO trial.

Incidence of all-cause hospitalization was similar between both groups in both trials, with 2,836 (43.5%) patients and 2,926 (45.0%) patients hospitalized for any cause in the finerenone and placebo groups, respectively. More hospitalizations were non-cardiovascular-related

(35% in both finerenone and placebo groups) versus cardiovascular-related (19% in the finerenone group and 20% in the placebo groups). Comparing the finerenone group with the placebo group, the HR was 0.95 (95% CI, 0.88 to 1.02) in the FIDELIO trial and 0.97 (95% CI, 0.90 to 1.04) in the FIGARO trial.

At baseline, the mean KDQOL-36 summary scores in all domains were comparable between treatment groups in each trial; between both trials, except for the “burden of kidney disease” domain for which patients in the FIGARO group scored relatively higher than those in the FIDELIO group. Quality of life decreased over time for all patients consistently in all domains, and it was assessed until month 36 in the FIDELIO trial and month 48 in the FIGARO trial. The physical component summary showed a sustained difference in favour of finerenone in the FIDELIO trial at month 12 (LS mean difference = [REDACTED]) and month 24 (LS mean difference = [REDACTED]), and in the FIGARO trial at month 36 (LS mean difference = [REDACTED]).

## Harms Results

A total of 5,602 (86.1%) patients in the finerenone group and 5,607 (86.4%) patients in the placebo group experienced at least 1 AE. The most common AE in the finerenone group was hyperkalemia (14% vs. 6.9% in the placebo group), and the most common AEs in the placebo group were hypertension (9% vs. 6.4% in the finerenone group) and peripheral edema (5.9% vs. 9% in the finerenone group). A total of 2,060 (31.6%) patients in the finerenone group and 2,186 (33.7%) in the placebo group experienced at least 1 serious AE. The most commonly reported serious AE was pneumonia (2.2% in the finerenone group vs. 3.3% in the placebo group).

A total of 414 (6.4%) patients in the finerenone group and 351 (5.4%) in the placebo group stopped treatment due to AEs. There was a total of 110 (1.7%) deaths and 151 (2.3%) deaths due to treatment-emergent AEs in the finerenone and placebo groups, respectively.

In terms of notable harms, more patients reported hypotension in the finerenone group than in the placebo group (4.6% vs. 3.9%). The number of patients who experienced atrial flutter and atrial fibrillation was less than 1% in each treatment group and comparable between groups. The number of patients who experienced hospitalization due to hyperkalemia was higher in the finerenone group compared to the placebo group (0.9% vs. 0.2%).

## Critical Appraisal

Key baseline demographic and disease characteristics and past history of medication used appeared to be balanced between the finerenone and placebo groups in both trials. There were important protocol deviations, balanced between treatment groups, reported in 53% and 58.5% of patients in the FIDELIO and FIGARO trials, respectively. Due to study timelines, more protocol deviations associated with the COVID-19 pandemic were reported in the FIGARO trial than the FIDELIO trial; however, deviations were balanced between treatment groups and supportive analyses did not uncover any notable effect of the COVID-19 pandemic on the treatment effect of finerenone. The interpretation of results for the HRQoL instruments (i.e., the ability to assess trends over time and to make comparisons across treatment groups) is limited by the significant decline in patients available to provide assessment over time as well as lack of evidence of validity or minimally important difference of the HRQoL questionnaires used in the trials in patients with CKD and T2D. In the prespecified FIDELITY pooled analysis combining both trials, patients in the FIDELIO trial had a lower eGFR at baseline than those in the FIGARO trial and the mean treatment duration was longer in the FIGARO

trial (approximately 35 months) than in the FIDELIO trial (approximately 27 months). The FIDELITY statistical analysis was exploratory and descriptive in nature, with no adjustment for multiplicity; however, pooling is considered appropriate.

According to the clinical experts consulted by CADTH for this review, the demographic and disease characteristics of both study populations were generally reflective of the Canadian population with CKD and T2D. They agreed that there was an overrepresentation of male patients (70% males to 30% females), whereas they noted there should be a more proportionate representation of patients because of the potential differences in treatment efficacy and safety. The product monograph of finerenone indicates that patients with an eGFR of 25 mL/min/1.73 m<sup>2</sup> or less should not start finerenone; however, 2.4% of patients in the FIDELIO study reported a baseline eGFR of 25 mL/min/1.73 m<sup>2</sup> or less (potentially due to decline in eGFR between screening and randomization). Although the trials were under way, the SOC for patients with CKD and T2D evolved to include an SGLT2 inhibitor. Therefore, only 6.7% of patients in both trials (n = 877) were on an SGLT2 inhibitor at baseline, and patients were not stratified by SGLT2 inhibitor use, but use at baseline was balanced between the 2 treatment groups in both trials. The clinical experts consulted by CADTH agreed that placebo plus SOC was an appropriate comparator in Canadian clinical practice for patients with CKD and T2D. The clinical experts noted that SOC would include ACE inhibitors or ARBs and ideally an SGLT2 inhibitors, which is still not widely accessible to patients with CKD and T2D living in Canada. The clinical experts pointed out that a combination therapy with the 2 drugs makes physiological sense because SGLT2 inhibitors are linked to reductions in the risk of hyperkalemic episodes (serum potassium  $\geq$  6.0 mmol/L), and finerenone has hyperkalemia as a side effect. There is, however, limited evidence on the positioning of finerenone compared with SGLT2 inhibitors, and the evidence available for the addition of finerenone to ACE inhibitor or ARB and a SGLT2 inhibitor is limited. A non-sponsor-submitted Reimbursement Review assessing the use of SGLT2 inhibitors in patients with CKD and T2D is currently ongoing. A phase II randomized controlled trial (RCT) that will compare finerenone plus placebo, SGLT2 inhibitors plus placebo, and finerenone plus SGLT2 inhibitors (CONFIDENCE trial) which was initiated in 2022, and results may provide more insight into this comparison and the place in therapy of finerenone. Finally, the trials included composite renal and cardiovascular outcomes and were only powered for their respective primary composite outcomes and not to the components of the primary outcome, which include a sustained decrease in eGFR and initiation of ESKD in the FIDELIO trial, and hospitalization due to heart failure in the FIGARO trial, hence the impact of finerenone on each of the components of the composite outcomes is uncertain.

## Indirect Comparisons

Indirect evidence from 1 published NMA by Zhao et al. (2022) evaluated the effectiveness of finerenone compared with SGLT2 inhibitors in the treatment of CKD and T2D. SGLT2 inhibitors are currently part of the SOC for patients with diabetic kidney disease; however, only 6.7% (877 of 13,026) of patients in the FIDELIO and FIGARO trials were concurrently taking SGLT2 inhibitors. This NMA, therefore, provides an indirect comparison of efficacy outcomes between finerenone and SGLT2 inhibitors.

## Description of Studies

The authors include 14 articles reporting 8 placebo-controlled RCTs comprising 30,661 patients. Seven studies involved an assessment of an SGLT2 inhibitor (13,246 patients receiving gliflozin vs. 11,741 receiving placebo); the EMPA-REG OUTCOME, CANVAS Program,

CREDESCENCE, DECLARE–TIMI 58, DAPA-CKD, VERTIS CV, and SCORED trials. One study (the pivotal FIDELIO trial) assessed finerenone (2,833 patients receiving finerenone vs. 2,841 receiving placebo). According to the risk of bias assessment, there was a low risk of bias in all 8 studies.

Major adverse cardiovascular event outcome was defined consistently across the included studies. Kidney function progression; however, was defined differently across the included studies, with composite end points that included ESKD, renal death, and sustained decrease in eGFR that ranged from 40% to 50%. One trial included patients who had initiated renal replacement therapy (EMPA-REG OUTCOME) and 2 trials included patients with kidney transplants (DAPA-CKD and SCORED). One trial (VERTIS CV) did not report a renal composite end point. The authors considered these definitions similar enough to be used in the meta-analysis.

### **Efficacy Results**

NMA results showed that, compared to finerenone, SGLT2 inhibitors significantly reduced the risks of kidney function progression (HR = 0.78; 95% CI, 0.67 to 0.90) and hospitalization for heart failure (HR = 0.71; 95% CI, 0.55 to 0.92). No treatment was favoured when finerenone was compared with SGLT2 inhibitors for the outcomes of major adverse cardiovascular events (HR = 0.95; 95% CI, 0.71 to 1.27), nonfatal MI (HR = 0.91; 95% CI, 0.64 to 1.30), nonfatal stroke (HR = 0.70; 95% CI, 0.35 to 1.39), cardiovascular death (HR = 1.00; 95% CI, 0.78 to 1.29), and all-cause death (HR = 0.96; 95% CI, 0.75 to 1.23). Network plots for all outcomes did not have any closed loop, suggesting a lack of direct evidence between finerenone and SGLT inhibitors, so an inconsistency test was not performed.

### **Harms Results**

The safety outcomes of both treatments were not assessed in this NMA.

### **Critical Appraisal**

This NMA included a limited number of studies with some heterogeneity in the definition a key renal outcome across the studies. Only 1 study assessed finerenone whereas the other 7 assessed an SGLT2 inhibitor, which limited the statistical power of this NMA. The second pivotal RCT on finerenone from this review (FIGARO) was not included in this NMA and may have strengthened this analysis. The authors did not explore the baseline demographic characteristics of the patient populations across the trials and reported that “the cardiorenal risk of participants was possibly different among included trials.” The durations of the trials were not reported and may have differed between studies. Moreover, the safety outcomes of both treatments were not assessed in this NMA. The CADTH review team was unable to rigorously assess the methods in this article because insufficient details on the methods were provided (e.g., no details on the retrieved number of records in the systematic review), and there was no discussion on possible adjustments for potential effect modifiers or feasibility assessment. A small proportion of patients in the included FIDELIO trial were using an SGLT2 inhibitor at baseline, but no additional analysis including and excluding this subgroup was conducted.

## Economic Evidence

**Table 3: Cost and Cost-Effectiveness**

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Health Canada indication: Adults with CKD and T2D Reimbursement request: Adults with CKD and T2D as an adjunct to SOC that consists of an ACE inhibitor or ARB and a SGLT2 inhibitor, unless contraindicated or not tolerated.
Treatment	Finerenone plus SOC
Dose regimen	Starting: <ul style="list-style-type: none"> <li>• 20 mg once daily if eGFR <math>\geq</math> 60 mL/min/1.73 m<sup>2</sup></li> <li>• 10 mg once daily if eGFR <math>\geq</math> 25 to &lt; 60 mL/min/1.73 m<sup>2</sup></li> </ul> Target: <ul style="list-style-type: none"> <li>• 20 mg once daily</li> </ul>
Submitted price	Finerenone, 10 mg, tablet: \$3.3400 Finerenone, 20 mg, tablet: \$3.3400
Treatment cost	\$1,219 annually
Comparator	SOC (consisting of an ACE inhibitor or ARB and a SGLT2 inhibitor, unless contraindicated or not tolerated) along with other concomitant medications for glucose management and/or cardiovascular complications (e.g., BB, diuretics, calcium antagonists, statins, platelet aggregation inhibitors, insulin, metformin, acarbose, sulfonyleurea, DPP-4 inhibitors, GLP-1 agonists)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (35.2 years)
Key data source	FIDELITY, a prespecified pooled efficacy and safety analysis combining data from FIDELIO-DKD and FIGARO-DKD (NCT02545049), 2 phase III, randomized, double-blind, placebo-controlled, multicentre clinical trials designed to investigate the effect of finerenone on reducing kidney failure and disease progression and on reducing CV mortality and morbidity, respectively.
Key limitations	<ul style="list-style-type: none"> <li>• The sponsor’s model structure may not adequately reflect the progressive nature of CKD. The model allows for substantial improvements in kidney function resulting in reduced mortality risk and improved quality of life, contrary to what would be expected in this disease area. The model predicts that patients may have improved kidney function (measured through sustained improvements in eGFR score) to the extent that an individual with an eGFR &lt; 15 mL/min/1.73 m<sup>2</sup> may return to normal kidney function. This was considered highly unlikely by CADTH clinical experts.</li> <li>• The influence of SGLT2 inhibitor as a component of SOC is uncertain. If SGLT2 inhibitors are to become SOC for this indication, it is unclear what the additional benefit of finerenone will be. In the trials, only 6.7% of patients were on SGLT2 inhibitors; therefore, there is not sufficient evidence to conclude what the relative and absolute risk reduction, regarding clinical parameters reviewed in the trial, would be for those also receiving finerenone.</li> <li>• The effect on dialysis reduction is uncertain. In the model, patients on finerenone progress at a slower rate to CKD stage 5, at which point dialysis is initiated – meaning patients on finerenone are less likely to receive dialysis. Further, patients who reach CKD5 while on finerenone were also assumed to have</li> </ul>

Component	Description
	<p>a lower risk of requiring dialysis, further reducing the rate of dialysis. It is unclear to what degree the clinical data support the latter assumption.</p> <ul style="list-style-type: none"> <li>• The effect on mortality is uncertain because the trials showed no statistically significant mortality reduction in the finerenone arm relative to placebo.</li> <li>• In the model, the sponsor assumed a reduction in MIs and stroke for patients on finerenone, which was not seen in the trials. The sponsor assumed that the HR for any CV event from the trials would apply to all individual CV events, such that finerenone would reduce all CV events equally. This was not observed for the individual CV outcomes from the trial in which statistically significant reductions in HF hospitalizations were seen but there were limited to no reductions in MIs and strokes.</li> <li>• Health state utility values derived from the trial were consistently higher than those seen in the literature for CKD, especially given the population being analyzed also has T2D as a comorbidity.</li> <li>• Health state costs for CKD states exclude relevant health system costs. This overestimates the predicted cost savings generated from finerenone usage.</li> </ul>
<p><b>CADTH reanalysis results</b></p>	<ul style="list-style-type: none"> <li>• CADTH was unable to conduct a base-case analysis because key limitations within the analysis could not be addressed given the structure of the model and available clinical information. CADTH notes these limitations likely favour finerenone, therefore the exploratory analyses performed by CADTH likely underestimate the true ICER.</li> <li>• Due to uncertainty regarding concurrent use of finerenone with SGLT2 inhibitors, CADTH was unable to conduct a reliable reanalysis in the reimbursement request population. Instead, all reanalyses are reflective of the proposed Health Canada indication population.</li> <li>• CADTH conducted 5 exploratory reanalyses: In exploratory reanalysis 1, CADTH used health state utility values from the literature, updated CKD state costs and aligned dialysis prevention in CKD 5 with that from the trial; in exploratory reanalysis 2, CADTH further removed MIs and strokes from the analysis; in reanalysis 3, CADTH further removed finerenone's benefit on CV death; in reanalysis 4, CADTH further assumed no reduction in dialysis for those who reach CKD 5; in exploratory reanalysis 5, CADTH further assumed both a lower rate of dialysis reduction and no CV death benefit from finerenone. <ul style="list-style-type: none"> <li>◦ Reanalysis 1: ICER of \$70,052 per QALY gained (incremental costs: \$6,406; incremental QALYs: 0.09), 23% price reduction needed to achieve an ICER &lt; \$50,000 per QALY</li> <li>◦ Reanalysis 2: ICER of \$73,484 per QALY gained (incremental costs: \$6,935; incremental QALYs: 0.09), 29% price reduction needed to achieve an ICER &lt; \$50,000 per QALY</li> <li>◦ Reanalysis 3: ICER of \$175,549 per QALY gained (incremental costs: \$3,293; incremental QALYs: 0.02), 31% price reduction needed to achieve an ICER &lt; \$50,000 per QALY</li> <li>◦ Reanalysis 4: ICER of \$93,752 per QALY gained (incremental costs: \$7,333; incremental QALYs: 0.08), 44% price reduction needed to achieve an ICER &lt; \$50,000 per QALY</li> <li>◦ Reanalysis 5: ICER of \$2,994,490 per QALY gained (incremental costs: \$4,256; incremental QALYs: &gt; 0.01), 55% price reduction needed to achieve an ICER &lt; \$50,000 per QALY</li> </ul> </li> </ul>

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BB = beta blockers; CKD = chronic kidney disease; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide 1; HF = heart failure; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; LY = life-year; MI = myocardial infarction; QALY = quality-adjusted life-year; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes.

## Budget Impact

CADTH's reanalyses of the sponsor submitted budget impact assumed patients with T2D and CKD with concomitant chronic HF would be eligible for finerenone and the reanalyses included mark-ups and dispensing fees. CADTH reanalyses suggest that the overall budget impact to the public drug plans of reimbursing finerenone in the Health Canada indication, regardless of what constituted SOC, is expected to be \$148,282,507 over 3 years (year 1: \$17,075,144; year 2: \$49,750,884; year 3: \$81,456,478).

## Request for Reconsideration

The sponsor filed a Request for Reconsideration for the draft recommendation for finerenone for the treatment of CKD and T2D. In their request, the sponsor objected to the condition in the CDEC draft recommendation that treatment with finerenone must not be reimbursed in patients “receiving a SGLT2 inhibitor regardless of indication” for the following reasons:

- it is not supported by the evidence identified within the clinical submission and the clinical review report
- the focus on the SGLT2 inhibitor subgroup is an erroneous, arbitrary, and inconsistent decision
- draft recommendation is contrary to clinical expert opinion and all recent clinical guidelines
- exclusion of patients who are receiving an SGLT2 inhibitor is inequitable.

In the meeting to discuss the sponsor’s request for reconsideration, CDEC considered the following information:

- feedback from the sponsor
- information from the initial submission relating to the issues identified by the sponsor
- feedback from 2 clinical specialists with expertise in the diagnosis and management of CKD and cardiovascular disease
- feedback from the public drug plans
- feedback from 33 clinician groups comprising 159 individual clinicians.

All stakeholder feedback received in response to the draft recommendation from clinician groups and the public drug programs is available on the CADTH website.

## CDEC Information

### Initial Meeting Date: October 27, 2022

#### Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunskey, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

**Regrets:** One expert committee member did not attend

**Conflicts of interest:** None

### Reconsideration Meeting Date: February 22, 2023

#### Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunskey, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell,

Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

**Regrets:** Five expert committee members did not attend

**Conflicts of interest:** None